02-05-2010

10/598,789B Yong Chu ~~07-08-2008~~

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SESSION RESUMED IN FILE 'CAPLUS' AT 22:09:19 ON 08 JUL 2008
FILE 'CAPLUS' ENTERED AT 22:09:19 ON 08 JUL 2008
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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	92.96	520.51

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-12.80	-20.00

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(FILE 'HOME' ENTERED AT 21:14:57 ON 08 JUL 2008)

FILE 'REGISTRY' ENTERED AT 21:15:19 ON 08 JUL 2008
L1 STRUCTURE UPLOADED
L2 22 S L1
L3 STRUCTURE UPLOADED
L4 13 S L3
L5 11 S LL3 FULL
L6 343 S L3 FULL

FILE 'CAPLUS' ENTERED AT 21:26:04 ON 08 JUL 2008
L7 183 S L6

FILE 'REGISTRY' ENTERED AT 21:35:30 ON 08 JUL 2008
L8 STRUCTURE UPLOADED
L9 1 S L8
L10 39 S L8 FULL

FILE 'CAPLUS' ENTERED AT 21:37:13 ON 08 JUL 2008
L11 16 S L10

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	93.44	520.99

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FILE 'CAPLUS' ENTERED AT 22:09:48 ON 08 JUL 2008
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FILE COVERS 1907 - 8 Jul 2008 VOL 149 ISS 2
FILE LAST UPDATED: 7 Jul 2008 (20080707/ED)

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=> s l7 and alkylating and DNA
21821 ALKYLATING
902486 DNA
20200 DNAS
905661 DNA
(DNA OR DNAS)
L12 49 L7 AND ALKYLATING AND DNA

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L12 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d l12 not l11
L11 IS NOT VALID HERE
For an explanation, enter "HELP DISPLAY".

=> s l12 not l11
L13 37 L12 NOT L11

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67172 INDOLE
11317 INDOLES
69904 INDOLE
(INDOLE OR INDOLES)
L14 12 L13 AND INDOLE

=> d ibib abs hitstr tot

L14 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:873113 CAPLUS Full-text
DOCUMENT NUMBER: 147:258037
TITLE: Preparation of water-soluble CC-1065 analogs and their conjugates, especially peptidic and glycosidic prodrugs, for treating tumors

INVENTOR(S): Beusker, Patrick Henry; De Groot, Franciscus Marinus Hendrikus; Tietze, Lutz F.; Major, Felix; Joosten, Johannes Albertus Frederikus; Spijker, Henri Johannes

PATENT ASSIGNEE(S): Syntarga B.V., Neth.; Georg-August-Universitaet Goettingen Stiftung Oeffentlichen Rechts (Ohne Bereich Humanmedizin)

SOURCE: PCT Int. Appl., 149pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007089149	A2	20070809	WO 2007-NL50043	20070202
WO 2007089149	A3	20070927		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.: WO 2006-NL50020 A 20060202

OTHER SOURCE(S): MARPAT 147:258037

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to novel analogs of the DNA-binding alkylating agent CC-1065 of formula I (variables defined below) and to their conjugates, and to compds. of formula II as antitumor agents. Compds. I [Z = CHCHR1R2, CR3R3'; R1 = halo, OSO2Ra; Ra = (un)substituted perhalo/alkyl, benzyl, phenyl; R2 = H, (un)substituted alkyl; R3, R3', R4, R4' = independently H, (un)substituted alkyl, wherein .gtoreq. 2 of R2, R3, R3', R4, R4' are optionally joined to form .gtoreq.1 (un)substituted carbocycles or heterocycles; Y = CHR1, (CR3R3')n; n = 0-1; X2 = O, CH2 and derivs., , NH and derivs., :N, etc.; each R5, R5', R6, R6', R7, R7' = independently H, OH, SH, etc.; and/or R5R5', and/or R6R6', and/or R7R7' = independently :O, :S, :NH and derivs.; and/or R5' and R6', and/or R6' and R7' are absent; .gtoreq.2 of R5, R5', R6, R6', R7, R7' optionally being joined to form .gtoreq.1 (un)substituted aliph. or arom. carbocycles or heterocycles; X1 = O, S, NR13; R13 = H, (un)substituted alkyl; X3 = O, S, NH and derivs.; or X3 = -X3a or X3b- wherein X3a is connected to the carbon to which X4 is attached and selected from H, (un)substituted alkyl, acyl; X3b is connected to the Ph ring ortho to R10 and = R8; R8-R11 = independently H, OH, NH2, a water-sol. group, etc. provided that at least one of R8-R11 contains at least one water-sol. group; .gtoreq. 2 of R8-R11, or X3b optionally being joined to form .gtoreq.1 (un)substituted aliph. or arom. carbocycles or heterocycles; m = 0-1; q = 0-2; provided that at least one of R2-R5 and R3'-R5' is not H] were prepd. The invention also relates to V2-[L2-L-(V1-Y)a-(W)c]b [II; V2 = absent or a functional moiety; each L2 =

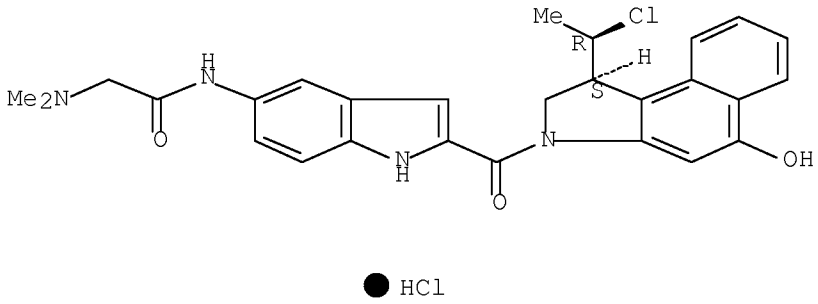
independently absent or a linking group linking V2 to L or to V1 or Y when L is absent; each L = independently absent or a linking group linking L2 or V2 when L2 is absent to one or more V1 and/or Y; each V1 = independently H, conditionally-cleavable or conditionally-transformable moiety, which can be cleaved or transformed by a chem., photochem., phys., biol., or enzymic process; each Y = independently absent or a self-eliminating spacer system contg. .gtoreq.1 self-elimination spacers (selected from NH-p-C6H4-CH2COO-, -NH-p-C6H4-CH:CHCH2OCO-, NH-p-C6H4-CH2, etc.) and is linked to V1, optionally L, and one or more W; each a, b = independently an integer; c = an integer .ltoreq. total no. of attachment sites for W in the one or more V1-Y moieties; each W = independently I wherein .gtoreq.1 of X1, R6-R11 may optionally in addn. be substituted by V2'-[L2'-L'-(V1'-Y')a'-(W)c'- 1]b'- (III); each V2', L2', L', V1', Y', Z', a', b', c' have the same meaning as defined for V2, L2, L, V1, Y, Z, a, b, c; .gtoreq.1 substituents of formula III being independently connected to .gtoreq.1 of X1, R6-R11 via Y' or V1' when Y' is absent, each Z being connected to Y or V1' when Y is absent through either X1 or an atom in R6-R11; provided that at least one of the one or more V1 and the one or more V1' is not H]. The conjugates are designed to release their (multiple) payload after one or more activation steps and/or at a rate and time span controlled by the conjugate to selectively deliver and/or controllably release one or more of said DNA alkylating agents. Thus, linker-agent conjugate IV was prepd. by a multi-step synthesis from (1S,10R)-1-(10-chloroethyl)-5-hydroxy-1,2-dihydro-3H-benz[e]indole , and its conjugation with herceptin antibody studied. Conjugate (1S, 10R)-V showed an IC50 = 7900 nM against A549 lung carcinoma cells in the absence of .beta.-D-galactosidase, and an IC50 = 1.2 nM in the presence of the enzyme, which gave a cytotoxicity quotient (QIC50) of 4800 in an in vitro assay. (+)-Anti-V was prepd. and evaluated in vivo in an orthotopic breast tumor SCID mouse model using the antibody-directed enzyme therapy (ADEPT) concept. Thus, two treatment cycles of a monoclonal antihuman urokinase plasminogen activator receptor antibody conjugated with .beta.-galactosidase (uPAR*.beta.-Gal) in phosphate-buffered saline, followed by 3 injections of conjugate (+)-anti-V resulted in an increased inhibitory effect on tumor growth, while no inhibitory effect was obsd. by using (uPAR*.beta.-Gal) or conjugate alone.

IT 945674-98-6P 945714-21-6P 945714-25-0P
945864-58-4P 945864-59-5P 945864-60-8P
945864-84-6P 945864-85-7P 945864-86-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of water-sol. CC-1065 analogs and their conjugates, esp. peptidic and glycosidic prodrugs, for tumor therapy)

RN 945674-98-6 CAPLUS

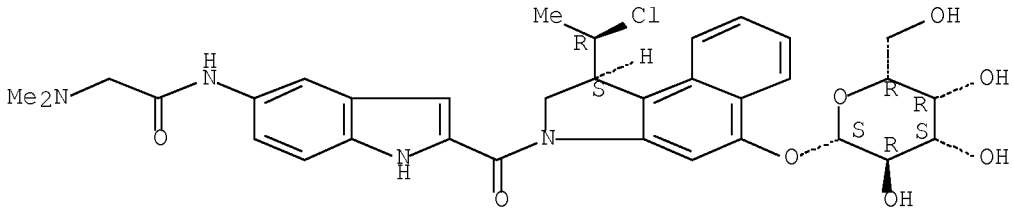
CN Acetamide, N-[2-[[(1S)-1-[(1R)-1-chloroethyl]-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-2-(dimethylamino)-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



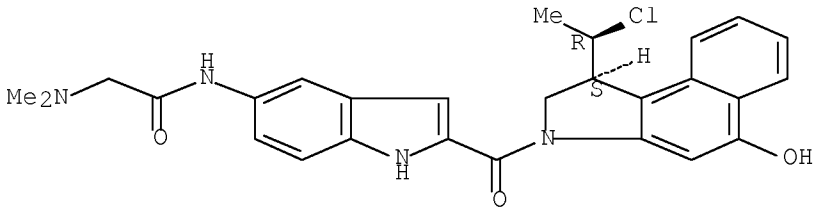
RN 945714-21-6 CAPLUS
CN Acetamide, N-[2-[[(1S)-1-[(1R)-1-chloroethyl]-5-(.beta.-D-galactopyranosyloxy)-1,2-dihydro-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-2-(dimethylamino)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



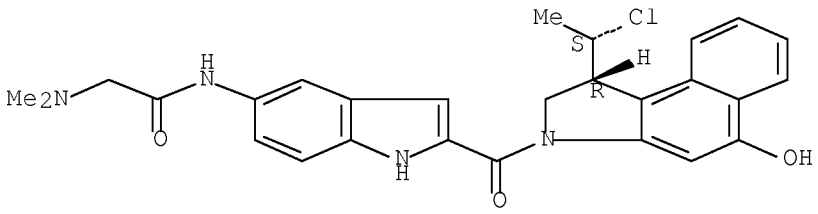
RN 945714-25-0 CAPLUS
CN Acetamide, N-[2-[[(1S)-1-[(1R)-1-chloroethyl]-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-2-(dimethylamino)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



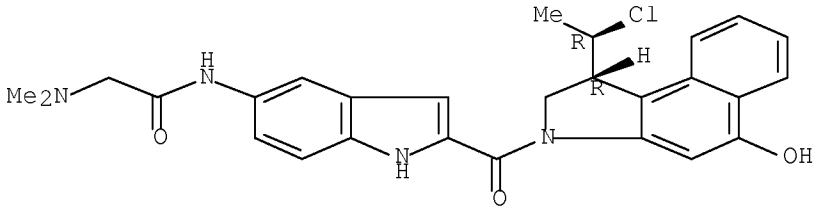
RN 945864-58-4 CAPLUS
CN Acetamide, N-[2-[[(1R)-1-[(1S)-1-chloroethyl]-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-2-(dimethylamino)- (CA INDEX NAME)

Absolute stereochemistry.



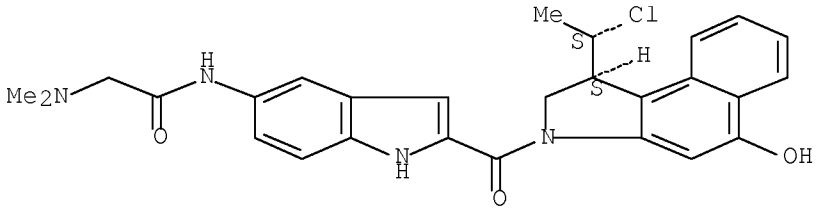
RN 945864-59-5 CAPLUS
CN Acetamide, N-[2-[[(1R)-1-[(1R)-1-chloroethyl]-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-2-(dimethylamino)- (CA INDEX NAME)

Absolute stereochemistry.



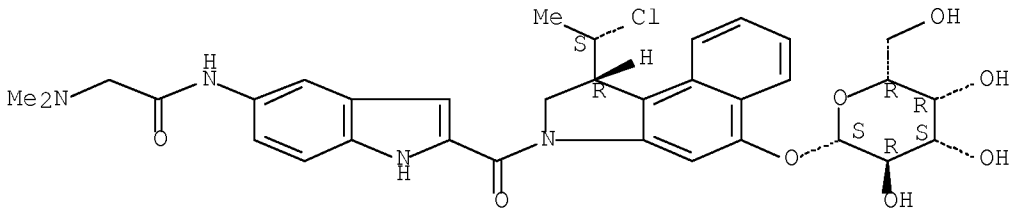
RN 945864-60-8 CAPLUS
CN Acetamide, N-[2-[[(1S)-1-[(1S)-1-chloroethyl]-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-2-(dimethylamino)- (CA INDEX NAME)

Absolute stereochemistry.



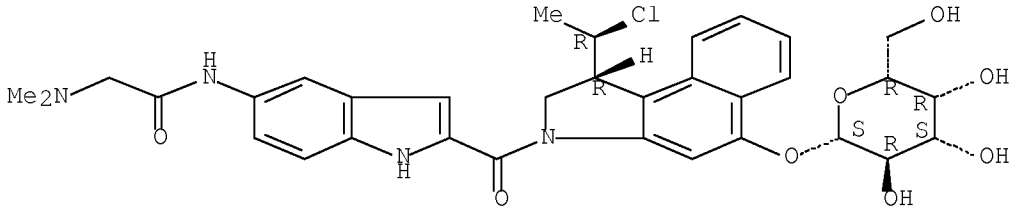
RN 945864-84-6 CAPLUS
CN Acetamide, N-[2-[[(1R)-1-[(1S)-1-chloroethyl]-5-(.beta.-D-galactopyranosyloxy)-1,2-dihydro-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-2-(dimethylamino)- (CA INDEX NAME)

Absolute stereochemistry.



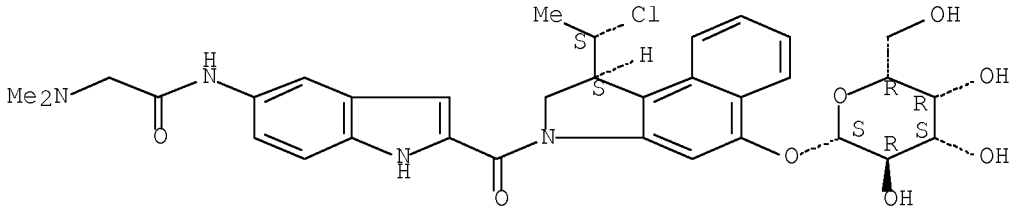
RN 945864-85-7 CAPLUS
CN Acetamide, N-[2-[[(1R)-1-[(1R)-1-chloroethyl]-5-(.beta.-D-galactopyranosyloxy)-1,2-dihydro-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-2-(dimethylamino)- (CA INDEX NAME)

Absolute stereochemistry.



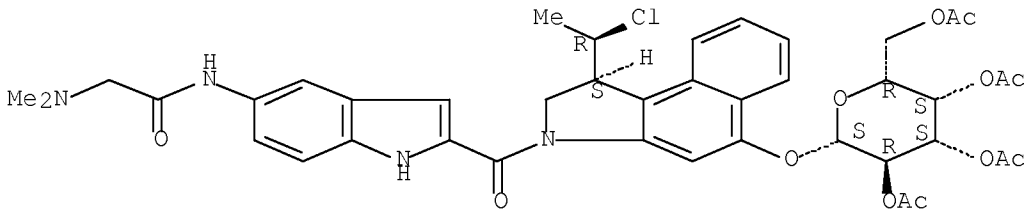
RN 945864-86-8 CAPLUS
CN Acetamide, N-[2-[[(1S)-1-[(1S)-1-chloroethyl]-5-(.beta.-D-galactopyranosyloxy)-1,2-dihydro-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-2-(dimethylamino)- (CA INDEX NAME)

Absolute stereochemistry.



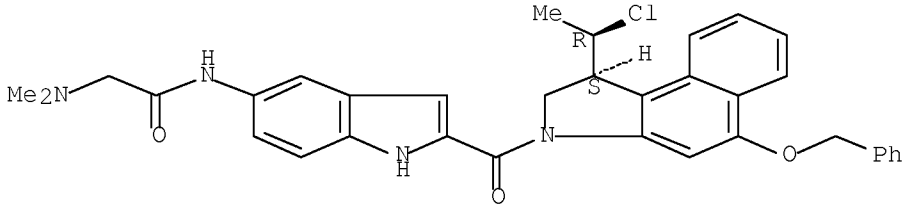
IT 945674-85-1P 945674-94-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of water-sol. CC-1065 analogs and their conjugates, esp. peptidic and glycosidic prodrugs, for tumor therapy)
RN 945674-85-1 CAPLUS
CN Acetamide, N-[2-[[(1S)-1-[(1R)-1-chloroethyl]-1,2-dihydro-5-[(2,3,4,6-tetra-O-acetyl-.beta.-D-galactopyranosyl)oxy]-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-2-(dimethylamino)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 945674-94-2 CAPLUS
CN Acetamide, N-[2-[[(1S)-1-[(1R)-1-chloroethyl]-1,2-dihydro-5-(phenylmethoxy)-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-2-(dimethylamino)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



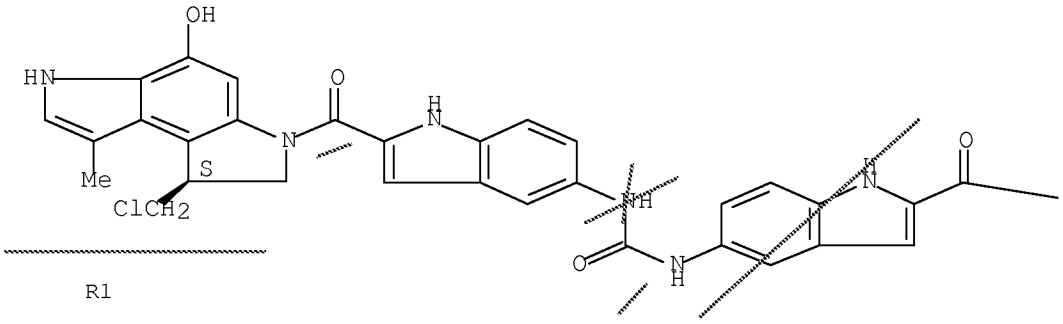
L14 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:863413 CAPLUS Full-text
DOCUMENT NUMBER: 138:164594
TITLE: Cell-free and Cellular Activities of a DNA Sequence Selective Hairpin Polyamide-CBI Conjugate
AUTHOR(S): Wang, Yong-Dong; Dziegielewski, Jaroslaw; Chang, Aileen Y.; Dervan, Peter B.; Beerman, Terry A.
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, Roswell Park Cancer Institute, Buffalo, NY, 14263, USA
SOURCE: Journal of Biological Chemistry (2002), 277(45), 42431-42437
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Alkylating agents are generally highly reactive with DNA but demonstrate limited DNA sequence selectivity. In contrast, synthetic pyrrole-imidazole polyamides recognize specific DNA sequences with high affinity but are unable to permanently damage DNA. An eight-ring hairpin polyamide conjugated to the alkylating moiety cyclopropylpyrroloindole, related to the natural product CC-1065, affords a conjugate 1-CBI (polyamide 1-CBI (1-(chloromethyl)-5-hydroxyl-1,2-dihydro-3H-benz[e]indole) conjugate), which binds to specific sequences in the minor groove of DNA and alkylates a single adenine flanking the polyamide binding site. In this study, we show that 1-CBI alkylates DNA in both plasmid and intracellular minichromosomal form and inhibits DNA replication under both cell-free and cellular conditions. In addn., it inhibits cell growth and arrests cells in the G2/M phase of the cell cycle.

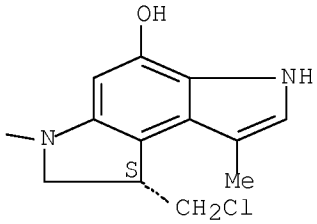
IT 129655-21-6, Bizelesin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cell growth inhibition induced by; inhibiting DNA replication and cell growth by cell-free and cellular activities of DNA sequence selective hairpin polyamide-CBI conjugate 1-CBI)
RN 129655-21-6 CAPLUS
CN Urea, N,N'-bis[2-[[(1S)-1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methylpyrrolo[3,2-e]indol-3(2H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:816666 CAPLUS Full-text
DOCUMENT NUMBER: 135:344632
TITLE: Selective Metal Cation Activation of a DNA Alkylating Agent: Synthesis and Evaluation of Methyl 1,2,9,9a-Tetrahydrocyclopropa[c]pyrido[3,2-e]indol-4-one-7-carboxylate (CPyI)
INVENTOR(S): Boger, Dale L.
PATENT ASSIGNEE(S): Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

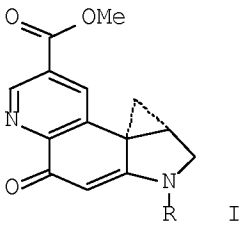
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001083482	A1	20011108	WO 2001-US14374	20010503

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-201543P P 20000503
OTHER SOURCE(S): MARPAT 135:344632
GI



I

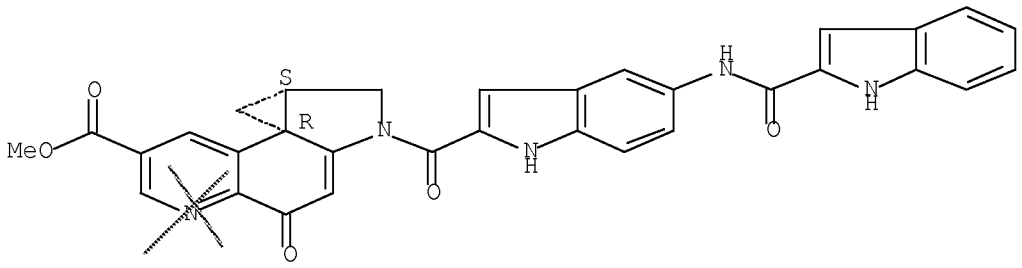
AB Title compds. I [R = 5,6,7-trimethoxyindol-2-ylcarbonyl, 5-methoxyindol-2-ylcarbonyl, indol-2-ylcarbonyl, etc.] were synthesized and shown to have DNA alkylation activity and cytotoxic activity that is susceptible to catalysis by metal ions, including Zn2+. The synthesis of I [CPyI, R = H; II], contg. a one carbon expansion of the C ring pyrrole found in the duocarmycin SA alkylation subunit and its incorporation into analogs of the natural product are detailed. The synthesis of II proceeded via a modified Skraup quinoline synthesis followed by a 5-exo-trig aryl radical cyclization onto an unactivated alkene with subsequent TEMPO trap or 5-exo-trig aryl radical cyclization onto a vinyl chloride for synthesis of the immediate precursor. Closure of the activated cyclopropane, accomplished by an Ar-3' spirocyclization, provided II in 10 steps and excellent overall conversion (29%). The evaluation of the CPyI-based agents revealed an intrinsic stability comparable to that of CC-1065 and duocarmycin A but that it is more reactive than duocarmycin SA and the CBI-based agents (3-4.times.). A pH-rate profile of the addn. of nucleophiles to CPyI demonstrated that an acid-catalyzed reaction is obsd. below pH 4 and that an uncatalyzed reaction predominates above pH 4. The expected predictable activation of CPyI by metal cations toward nucleophilic addn. was found to directly correspond to established stabilities of the metal complexes with the addn. product (Cu2+ > Ni2+ > Zn2+ > Mn2+ > Mg2+) and provides the opportunity to selectively activate the agents upon addn. of the appropriate Lewis acid. Resoln. and synthesis of a full set of natural product analogs and subsequent evaluation of their DNA alkylation properties revealed that the CPyI analogs retain identical DNA alkylation sequence selectivity and near-identical DNA

alkylation efficiencies compared to the natural products. Consistent with past studies and even with the deep-seated structural change in the alkylation subunit, the agents were found to exhibit potent cytotoxic activity that directly correlates with their inherent reactivity.

IT 280573-40-2P 280573-41-3P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(synthesis and evaluation of tetrahydrocyclopropapyridoindolone carboxylate as a DNA alkylating agent)

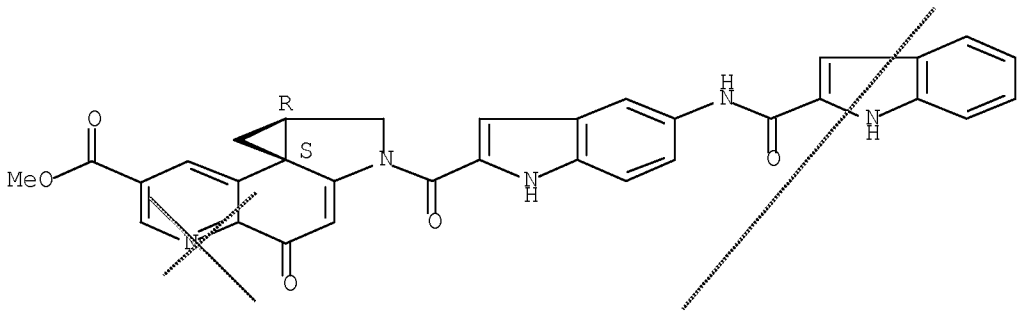
RN 280573-40-2 CAPLUS
CN 1H-Cyclopropa[3,4]pyrrolo[3,2-f]quinoline-7-carboxylic acid, 2,4,9,9a-tetrahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester, (8bR,9aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 280573-41-3 CAPLUS
CN 1H-Cyclopropa[3,4]pyrrolo[3,2-f]quinoline-7-carboxylic acid, 2,4,9,9a-tetrahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester, (8bS,9aR)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

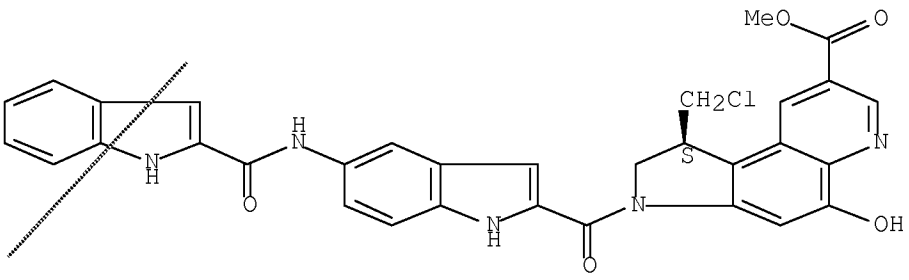


IT 280573-38-8P 280573-39-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(synthesis and evaluation of tetrahydrocyclopropapyridoindolone carboxylate as a DNA alkylating agent)

RN 280573-38-8 CAPLUS
CN 1H-Pyrrolo[3,2-f]quinoline-8-carboxylic acid, 1-(chloromethyl)-2,3-dihydro-

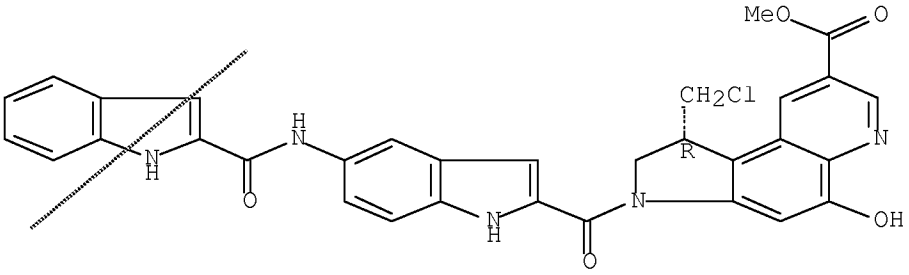
5-hydroxy-3-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-, methyl ester, (1S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

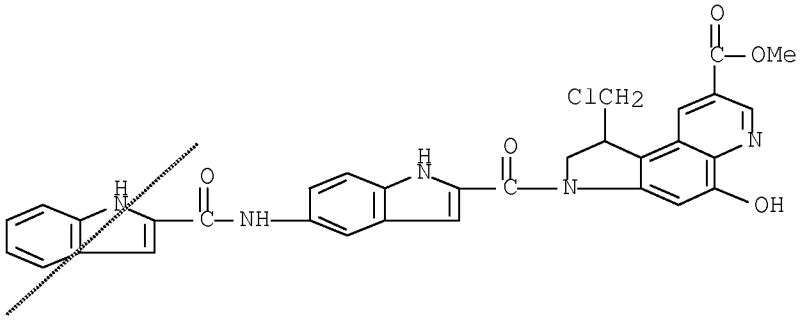


RN 280573-39-9 CAPLUS
CN 1H-Pyrrolo[3,2-f]quinoline-8-carboxylic acid, 1-(chloromethyl)-2,3-dihydro-5-hydroxy-3-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-, methyl ester, (1R)- (CA INDEX NAME)

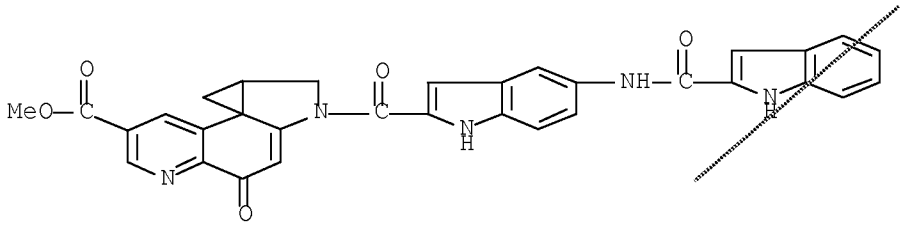
Absolute stereochemistry. Rotation (-).



IT 280573-18-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and evaluation of tetrahydrocyclopropapyridoindolone carboxylate as a DNA alkylating agent)
RN 280573-18-4 CAPLUS
CN 1H-Pyrrolo[3,2-f]quinoline-8-carboxylic acid, 1-(chloromethyl)-2,3-dihydro-5-hydroxy-3-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-, methyl ester (CA INDEX NAME)

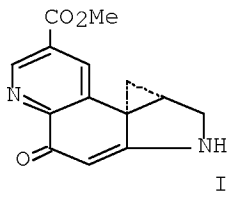


IT 280573-19-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis and evaluation of tetrahydrocyclopropapyridoindolone carboxylate as a DNA alkylating agent)
RN 280573-19-5 CAPLUS
CN 1H-Cyclopropa[3,4]pyrrolo[3,2-f]quinoline-7-carboxylic acid, 2,4,9,9a-tetrahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:301526 CAPLUS Full-text
DOCUMENT NUMBER: 133:89669
TITLE: Selective Metal Cation Activation of a DNA Alkylating Agent: Synthesis and Evaluation of Methyl 1,2,9,9a-Tetrahydrocyclopropa[c]pyrido[3,2-e]indol-4-one-7-carboxylate (CPyI)
AUTHOR(S): Boger, Dale L.; Boyce, Christopher W.
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of Organic Chemistry (2000), 65(13), 4088-4100
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:89669
GI



I

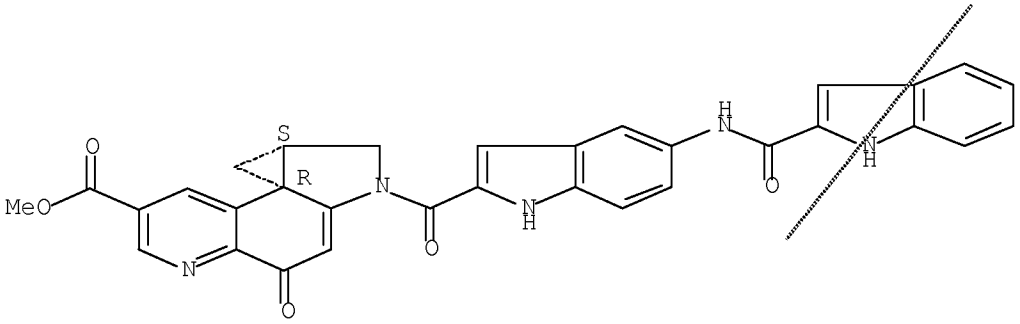
AB The synthesis of Me 1,2,9,9a-tetrahydrocyclopropa[c]pyrido[3,2-e]indol-4- one-7-carboxylate (CPyI) (I) contg. a one carbon expansion of the C ring pyrrole found in the duocarmycin SA alkylation subunit and its incorporation into analogs of the natural product are detailed. The unique 8-ketoquinoline structure of CPyI was expected to provide a tunable means to effect activation via selective metal cation complexation. The synthesis of CPyI was based on a modified Skraup quinoline synthesis followed by a 5-exo-trig aryl radical cyclization onto an unactivated alkene with subsequent TEMPO trap or 5-exo-trig aryl radical cyclization onto a vinyl chloride for synthesis of the immediate precursor. Closure of the activated cyclopropane, accomplished by an Ar-3' spirocyclization, provided the CPyI nucleus in 10 steps and excellent overall conversion (29%). The evaluation of the CPyI-based agents revealed an intrinsic stability comparable to that of CC-1065 and duocarmycin A but that it is more reactive than duocarmycin SA and the CBI-based agents (3-4.times.). A pH-rate profile of the addn. of nucleophiles to CPyI demonstrated that an acid-catalyzed reaction is obsd. below pH 4 and that an uncatalyzed reaction predominates above pH 4. The expected predictable activation of CPyI by metal cations toward nucleophilic addn. was found to directly correspond to established stabilities of the metal complexes with the addn. product (Cu2+ > Ni2+ > Zn2+ > Mn2+ > Mg2+) and provides the opportunity to selectively activate the agents upon addn. of the appropriate Lewis acid. This tunable metal cation activation of CPyI constitutes the first example of a new approach to in situ activation of a DNA binding agent complementary to the well-recognized methods of reductive, oxidative, or photochem. activation. Resoln. and synthesis of a full set of natural product analogs and subsequent evaluation of their DNA alkylation properties revealed that the CPyI analogs retain identical DNA alkylation sequence selectivity and near-identical DNA alkylation efficiencies compared to the natural products. Consistent with past studies and even with the deep-seated structural change in the alkylation subunit, the agents were found to exhibit potent cytotoxic activity that directly correlates with their inherent reactivity.

IT 280573-40-2P 280573-41-3P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(synthesis and evaluation of tetrahydrocyclopropapyridoindolone carboxylate as a DNA alkylating agent)

RN 280573-40-2 CAPLUS

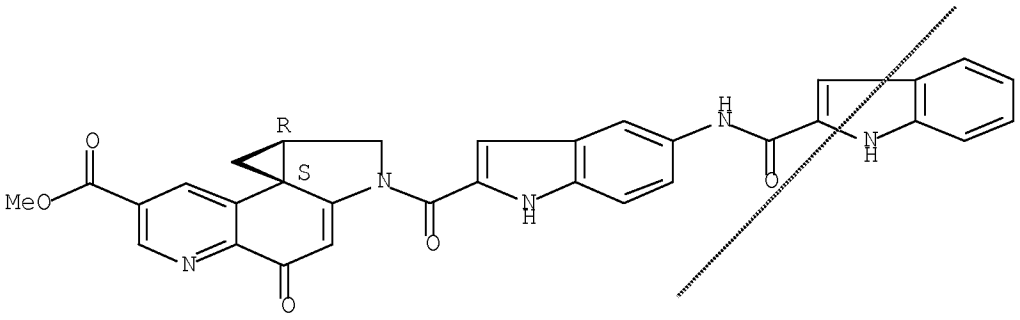
CN 1H-Cyclopropa[3,4]pyrrolo[3,2-f]quinoline-7-carboxylic acid, 2,4,9,9a-tetrahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester, (8bR,9aS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



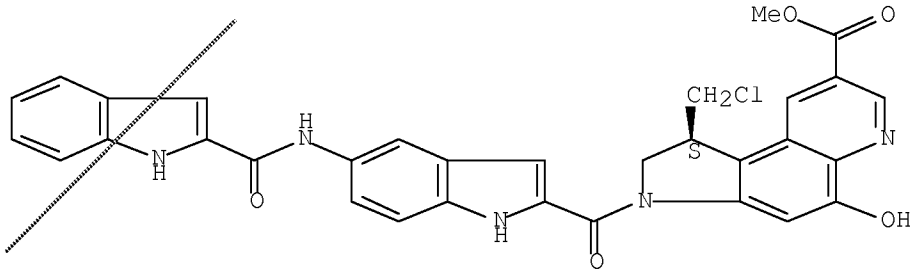
RN 280573-41-3 CAPLUS
CN 1H-Cyclopropa[3,4]pyrrolo[3,2-f]quinoline-7-carboxylic acid, 2,4,9,9a-tetrahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester, (8bS,9aR)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



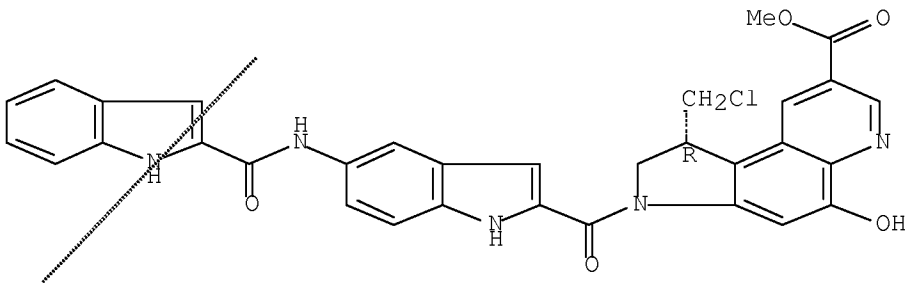
IT 280573-38-8P 280573-39-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(synthesis and evaluation of tetrahydrocyclopropapyridoindolone carboxylate as a DNA alkylating agent)
RN 280573-38-8 CAPLUS
CN 1H-Pyrrolo[3,2-f]quinoline-8-carboxylic acid, 1-(chloromethyl)-2,3-dihydro-5-hydroxy-3-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-, methyl ester, (1S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

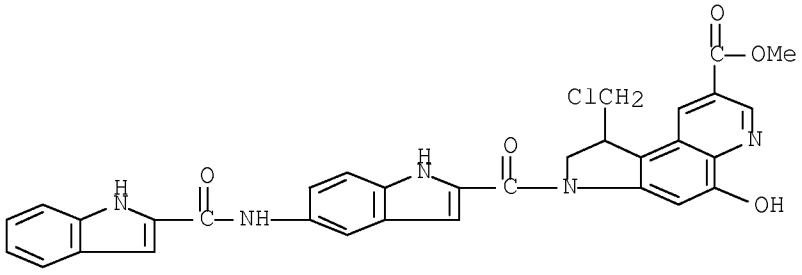


RN 280573-39-9 CAPLUS
CN 1H-Pyrrolo[3,2-f]quinoline-8-carboxylic acid, 1-(chloromethyl)-2,3-dihydro-5-hydroxy-3-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-, methyl ester, (1R)- (CA INDEX NAME)

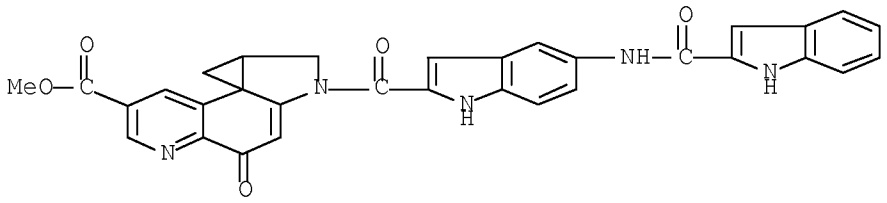
Absolute stereochemistry. Rotation (-).



IT 280573-18-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and evaluation of tetrahydrocyclopropapyridoindolone carboxylate as a DNA alkylating agent)
RN 280573-18-4 CAPLUS
CN 1H-Pyrrolo[3,2-f]quinoline-8-carboxylic acid, 1-(chloromethyl)-2,3-dihydro-5-hydroxy-3-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-, methyl ester (CA INDEX NAME)



IT 280573-19-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis and evaluation of tetrahydrocyclopropapyridoindolone carboxylate as a DNA alkylating agent)
RN 280573-19-5 CAPLUS
CN 1H-Cyclopropa[3,4]pyrrolo[3,2-f]quinoline-7-carboxylic acid, 2,4,9,9a-tetrahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester (CA INDEX NAME)



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:789131 CAPLUS Full-text
DOCUMENT NUMBER: 130:24911
TITLE: syntheses and cytotoxicities of analogs of duocarmycin and CC-1065
INVENTOR(S): Boger, Dale L.
PATENT ASSIGNEE(S): The Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9852925	A1	19981126	WO 1998-US10535	19980522
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2290789	A1	19981126	CA 1998-2290789	19980522
AU 9876927	A	19981211	AU 1998-76927	19980522
AU 754083	B2	20021107		
EP 983248	A1	20000308	EP 1998-924851	19980522
EP 983248	B1	20040714		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002503228	T	20020129	JP 1998-550697	19980522
NZ 500789	A	20020531	NZ 1998-500789	19980522
AT 271041	T	20040715	AT 1998-924851	19980522
US 6281354	B1	20010828	US 1999-423576	19991109

PRIORITY APPLN. INFO.: US 1997-48505P P 19970522
WO 1998-US10535 W 19980522

OTHER SOURCE(S): MARPAT 130:24911

AB Syntheses of analogs and derivs. of duocarmycin and CC-1065 are provided. Tabulations of their activities as antitumor antibiotics and as cell toxicity agents are presented as well as their sequences specific DNA alkylating activities.

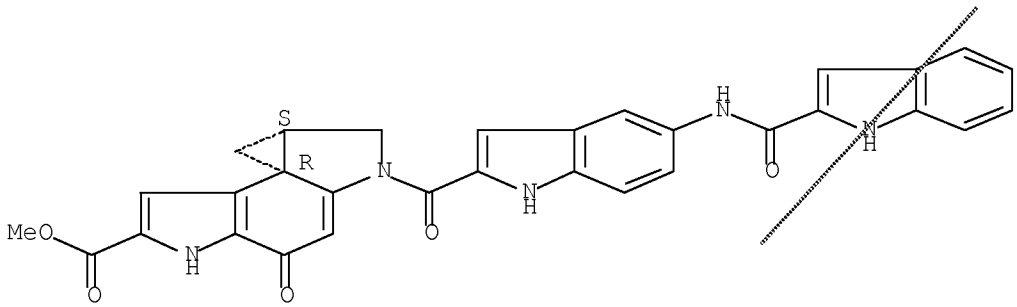
IT 190060-30-1P 190060-46-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(syntheses, DNA alkylating, antitumor antibiotic and cytotoxicities of analogs of duocarmycin and CC-1065)

RN 190060-30-1 CAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester, (7bR,8aS)- (CA INDEX NAME)

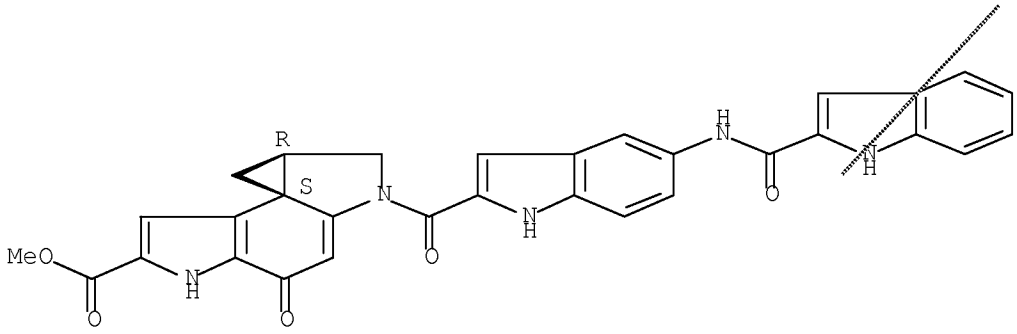
Absolute stereochemistry. Rotation (+).



RN 190060-46-9 CAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester, (7bS,8aR)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



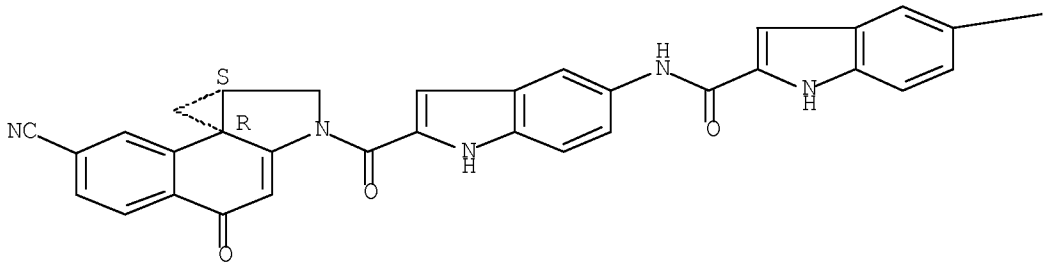
IT 216298-82-7, (+)-CCBI-indole2 216298-83-8, (+)-CBI-indole2 216298-84-9, (+)-MCBI-indole2 216298-85-0, (+)-CPI-indole2 216298-87-2, (-)-CCBI-indole2 216298-88-3 216298-89-4, (-)-MCBI-indole2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(syntheses, DNA alkylating, antitumor antibiotic and cytotoxicities of analogs of duocarmycin and CC-1065)

RN 216298-82-7 CAPLUS

CN 1H-Indole-2-carboxamide, 5-amino-N-[2-[[(8bR,9aS)-7-cyano-9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

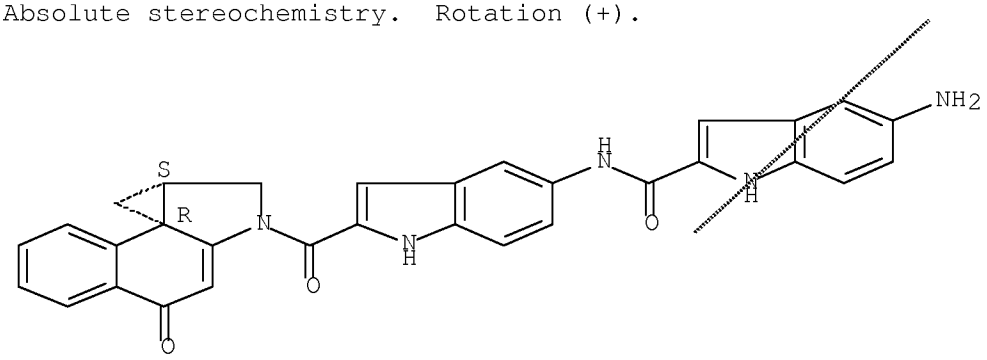
PAGE 1-A



PAGE 1-B

RN 216298-83-8 CAPLUS
CN 1H-Indole-2-carboxamide, 5-amino-N-[2-[[(8bR,9aS)-9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

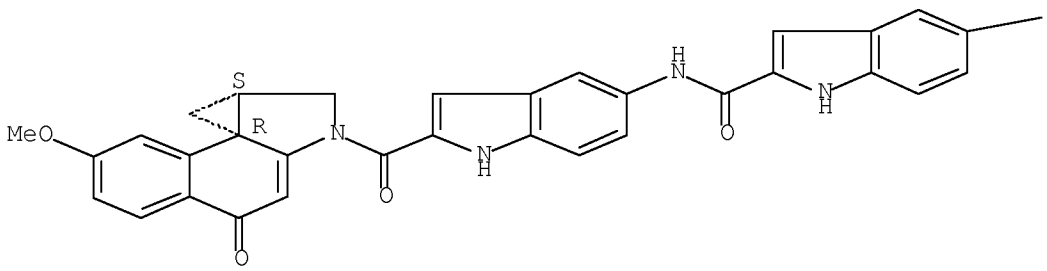
Absolute stereochemistry. Rotation (+).



RN 216298-84-9 CAPLUS
CN 1H-Indole-2-carboxamide, 5-amino-N-[2-[[(8bR,9aS)-9,9a-dihydro-7-methoxy-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

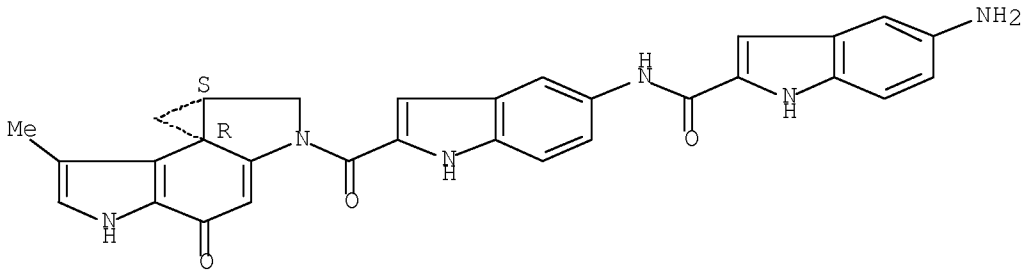
PAGE 1-A



PAGE 1-B

RN 216298-85-0 CAPLUS
CN 1H-Indole-2-carboxamide, 5-amino-N-[2-[[(1aS,8bR)-1a,2,5,6-tetrahydro-8-methyl-5-oxocyclopropa[c]pyrrolo[3,2-e]indol-3(1H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

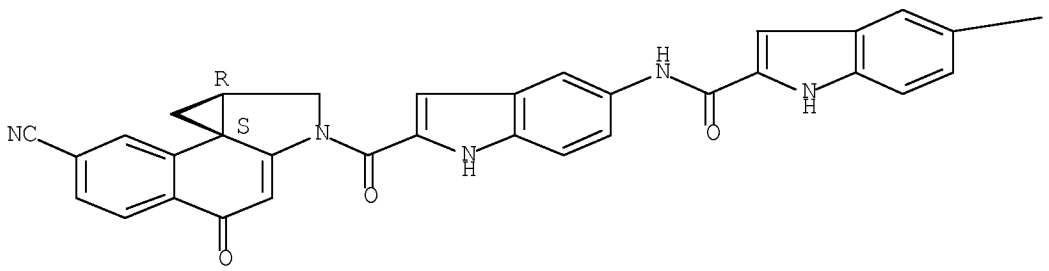
Absolute stereochemistry. Rotation (+).



RN 216298-87-2 CAPLUS
CN 1H-Indole-2-carboxamide, 5-amino-N-[2-[[(8bS,9aR)-7-cyano-9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

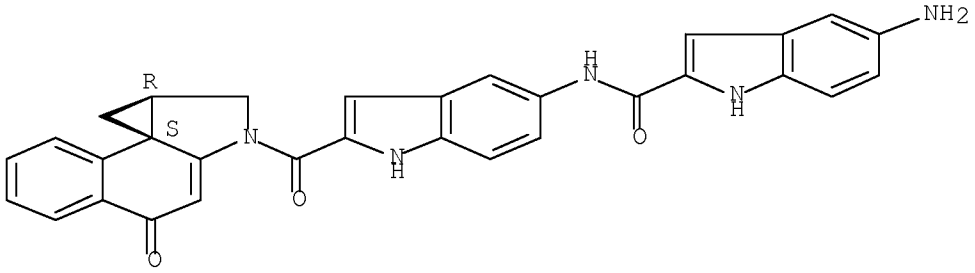
PAGE 1-A



PAGE 1-B

RN 216298-88-3 CAPLUS
CN 1H-Indole-2-carboxamide, 5-amino-N-[2-[[(8bS,9aR)-9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

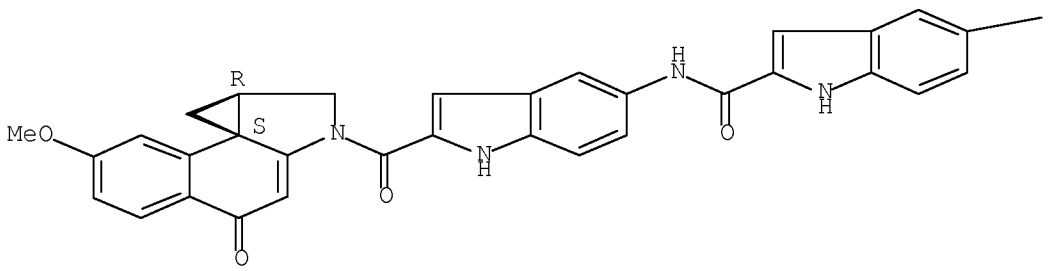
Absolute stereochemistry. Rotation (-).



RN 216298-89-4 CAPLUS
CN 1H-Indole-2-carboxamide, 5-amino-N-[2-[[(8bS,9aR)-9,9a-dihydro-7-methoxy-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

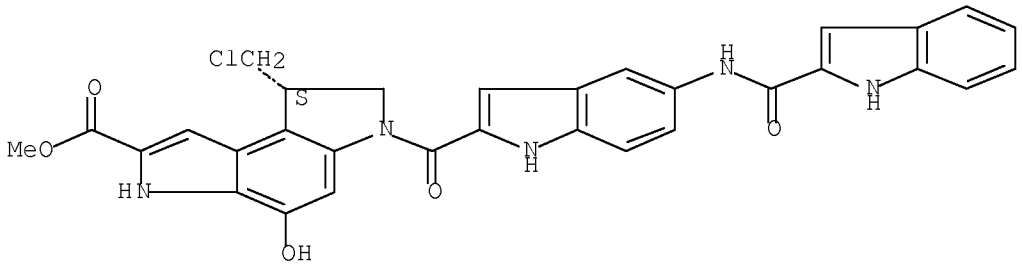


PAGE 1-B

IT 190060-28-7P 190060-44-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(syntheses, DNA alkylating, antitumor antibiotic and cytotoxicities of analogs of duocarmycin and CC-1065)

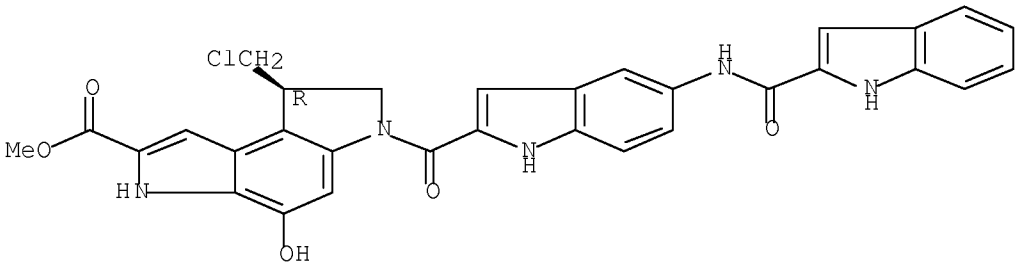
RN 190060-28-7 CAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-2-carboxylic acid, 8-(chloromethyl)-3,6,7,8-tetrahydro-4-hydroxy-6-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-, methyl ester, (8S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 190060-44-7 CAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-2-carboxylic acid, 8-(chloromethyl)-3,6,7,8-tetrahydro-4-hydroxy-6-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-, methyl ester, (8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



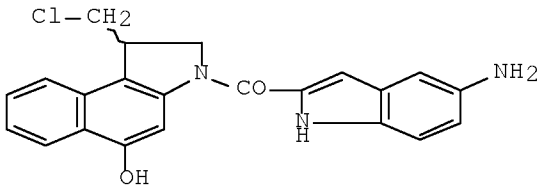
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1997:783786 CAPLUS Full-text
DOCUMENT NUMBER: 128:48468
ORIGINAL REFERENCE NO.: 128:9527a,9530a
TITLE: Preparation of DNA-binding glucuronide indoles immuno-conjugates as antitumors
INVENTOR(S): Wang, Yuqiang; Wright, Susan C.; Larrick, James W.
PATENT ASSIGNEE(S): Panorama Research, Inc., USA
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9744000	A2	19971127	WO 1997-US9055	19970522
WO 9744000	A3	19971231		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5843937	A	19981201	US 1996-652883	19960523
AU 9732170	A	19971209	AU 1997-32170	19970522
EP 918752	A2	19990602	EP 1997-927798	19970522
R: AT, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE				
CN 1219841	A	19990616	CN 1997-194862	19970522
JP 2000511893	T	20000912	JP 1997-542898	19970522

PRIORITY APPLN. INFO.: US 1996-652883 A 19960523
WO 1997-US9055 W 19970522

OTHER SOURCE(S): MARPAT 128:48468
GI



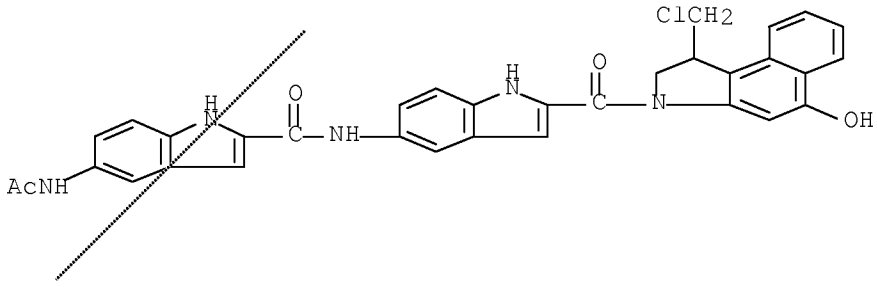
I

AB The present invention relates to novel DNA alkylating agents and the prodrugs of these agents which are useful as antitumors and DNA labeling agents. The compds. are hydroxydihydrobenzindole oligopeptides and prodrugs thereof wherein the monomeric constituents are derived from monocyclic, or bicyclic heterocyclic arom. residues. Thus, indole I was prepd. and tested for its antitumor activity with cytotoxicity (IC50 = 0.09 nM).

IT 199806-33-2P 199806-38-7P 199806-39-8P
199806-41-2P 199806-42-3P 199806-50-3P
199806-59-2P 199806-61-6P 199806-62-7DP,
monoclonal antibody conjugate 199806-64-9P 199806-65-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of DNA-binding glucuronide hydroxydihydrobenzindole oligopeptides immuno-conjugates as antitumors)

RN 199806-33-2 CAPLUS

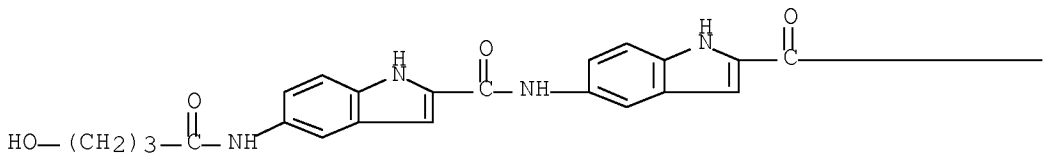
CN 1H-Indole-2-carboxamide, 5-(acetylamino)-N-[2-[[1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)



RN 199806-38-7 CAPLUS

CN 1H-Indole-2-carboxamide, N-[2-[[1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-5-[(4-hydroxy-1-oxobutyl)amino]- (CA INDEX NAME)

PAGE 1-A



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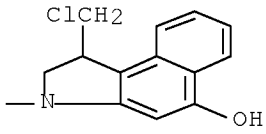
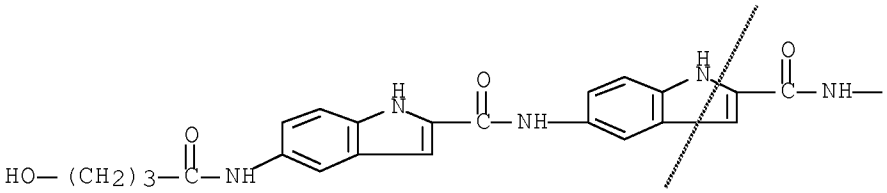


RN 199806-39-8 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[[2-[[1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]amino]carbonyl]-1H-indol-5-yl]-5-[(4-hydroxy-1-oxobutyl)amino]- (CA INDEX NAME)

PAGE 1-A



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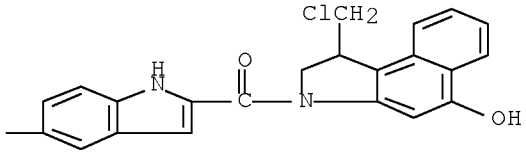
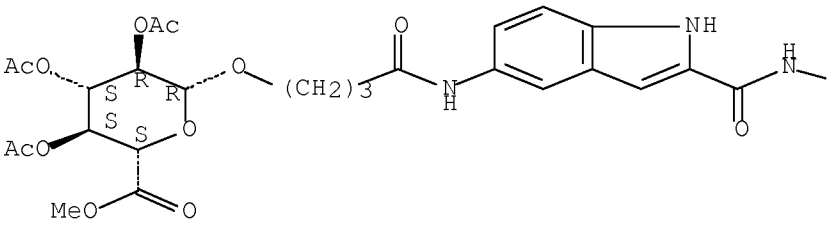


RN 199806-41-2 CAPLUS
CN .beta.-D-Glucopyranosiduronic acid, 4-[[2-[[[2-[[1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]amino]carbonyl]-1H-indol-5-yl]amino]-4-oxobutyl, methyl ester, 2,3,4-triacetate (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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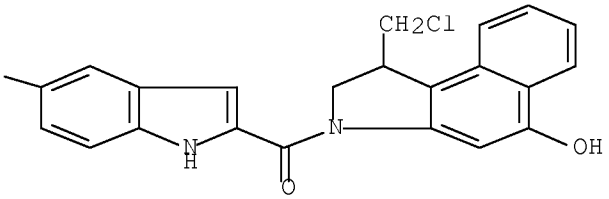
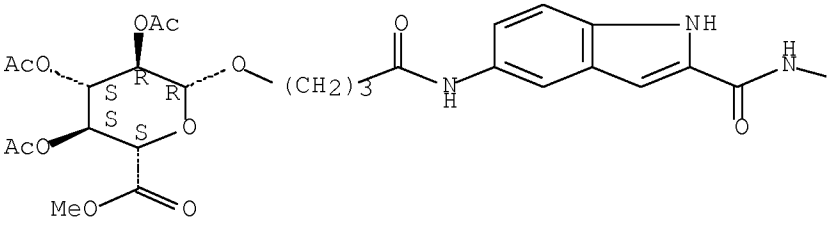


RN 199806-42-3 CAPLUS

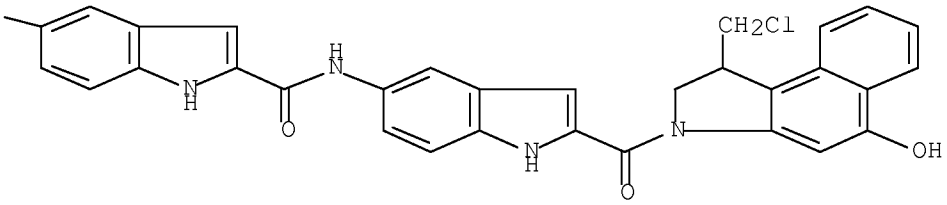
CN .beta.-D-Glucopyranosiduronic acid, 4-[[2-[[[2-[[[2-[[1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]amino]carbonyl]-1H-indol-5-yl]amino]carbonyl]-1H-indol-5-yl]amino]-4-oxobutyl, methyl ester, 2,3,4-triacetate (CA INDEX NAME)

Absolute stereochemistry.

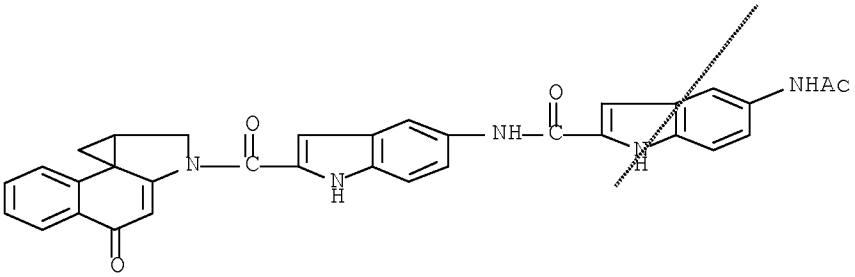
PAGE 1-A



PAGE 1-B

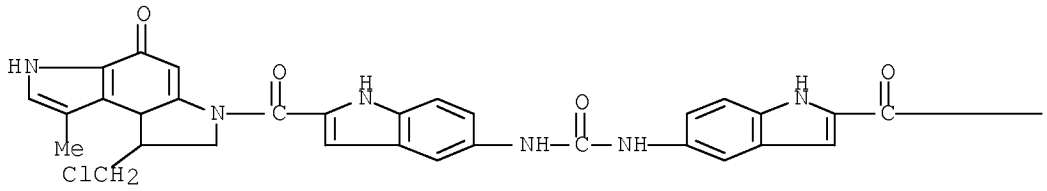


RN 199806-50-3 CAPLUS
CN 1H-Indole-2-carboxamide, 5-(acetylamino)-N-[2-[(9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

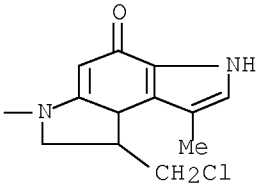


RN 199806-59-2 CAPLUS
CN Urea, N,N'-bis[2-[[1-(chloromethyl)-1,5,6,8b-tetrahydro-8-methyl-5-oxopyrrolo[3,2-e]indol-3(2H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

PAGE 1-A

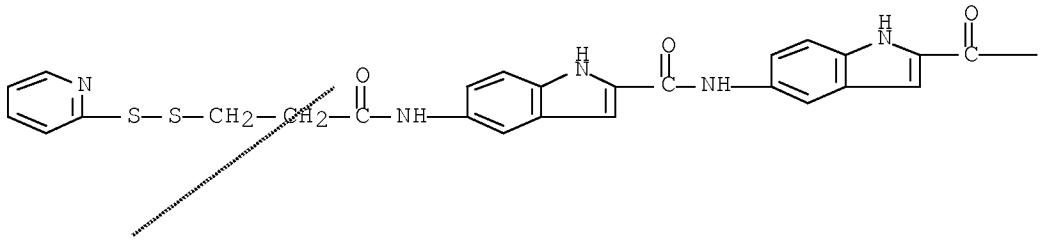


PAGE 1-B



RN 199806-61-6 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-5-[[1-oxo-3-(2-pyridinyldithio)propyl]amino]- (CA INDEX NAME)

PAGE 1-A



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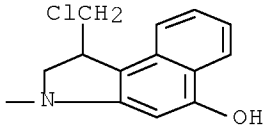
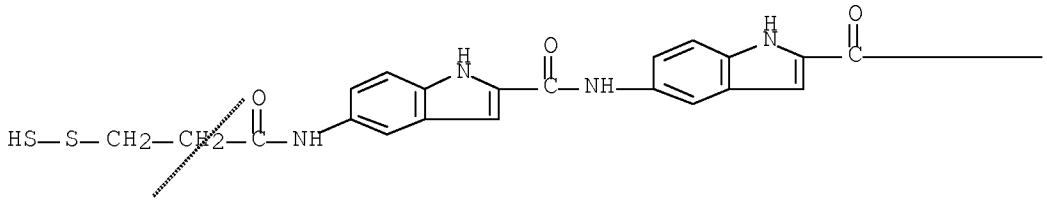
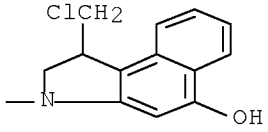


RN 199806-62-7 CAPLUS
CN 1-Propanesulfenothioic acid, 3-[[2-[[[2-[[1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]amino]carbonyl]-1H-indol-5-yl]amino]-3-oxo- (CA INDEX NAME)

PAGE 1-A



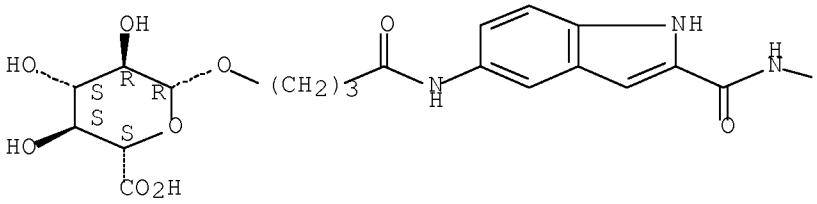
PAGE 1-B



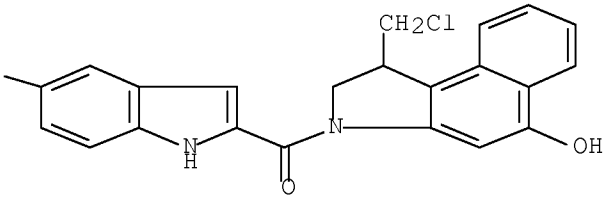
RN 199806-64-9 CAPLUS
CN .beta.-D-Glucopyranosiduronic acid, 4-[[2-[[[2-[[1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]amino]carbonyl]-1H-indol-5-yl]amino]-4-oxobutyl (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



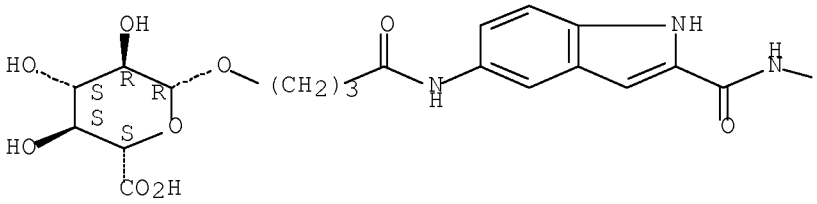
PAGE 1-B

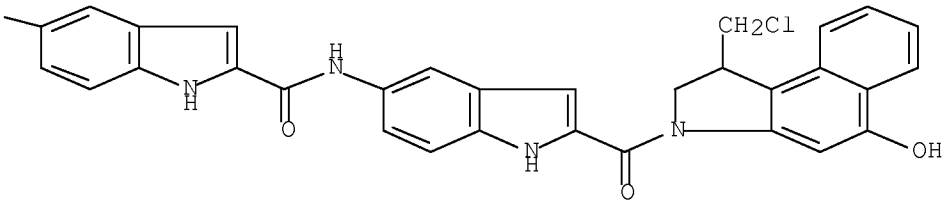


RN 199806-65-0 CAPLUS
CN .beta.-D-Glucopyranosiduronic acid, 4-[[2-[[[2-[[[2-[[1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]amino]carbonyl]-1H-indol-5-yl]amino]carbonyl]-1H-indol-5-yl]amino]-4-oxobutyl (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





L14 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1997:618073 CAPLUS Full-text
DOCUMENT NUMBER: 127:262561
ORIGINAL REFERENCE NO.: 127:51281a
TITLE: synthesis and DNA alkylating activity of MCBI analogs of CC-1065 and the duocarmycins
INVENTOR(S): Boger, Dale L.
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Boger, Dale L.
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9732850	A1	19970912	WO 1997-US3641	19970307
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2246783	A1	19970912	CA 1997-2246783	19970307
CA 2246783	C	20060711		
AU 9719902	A	19970922	AU 1997-19902	19970307
AU 711974	B2	19991028		
EP 888301	A1	19990107	EP 1997-908059	19970307
EP 888301	B1	20050810		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2000506168	T	20000523	JP 1997-531987	19970307
AT 301639	T	20050815	AT 1997-908059	19970307
ES 2244991	T3	20051216	ES 1997-908059	19970307
US 5985908	A	19991116	US 1998-142337	19980904
PRIORITY APPLN. INFO.:			US 1996-13024P P	19960308
			WO 1997-US3641 W	19970307

OTHER SOURCE(S): MARPAT 127:262561
GI

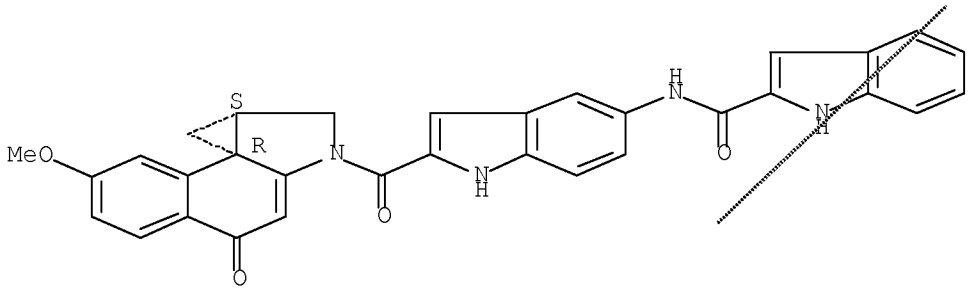
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB MCBI (7-methoxy-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one) (I) (R1 = H) is employable as a DNA alkylating agent and can be incorporated into analogs of CC-1065 and the duocarmycins I (R1 = Q1, Q2, Q3, Q4) for constructing regioselective DNA alkylating agents. Thus, I (R1 = Q1) (II) is prepd. by reacting 1-(chloromethyl)-5-hydroxy-8-methoxy-1,2-dihydro-3H-benz[e]indole with Q1-CO2H followed by cyclopropanation with NaH in THF-DMF. The relative rates of DNA alkylation do not follow the relative rates of acid-catalyzed solvolysis.

IT 173655-27-1P 173655-28-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and DNA alkylating activity of MCBI analogs of CC-1065 and the duocarmycins)

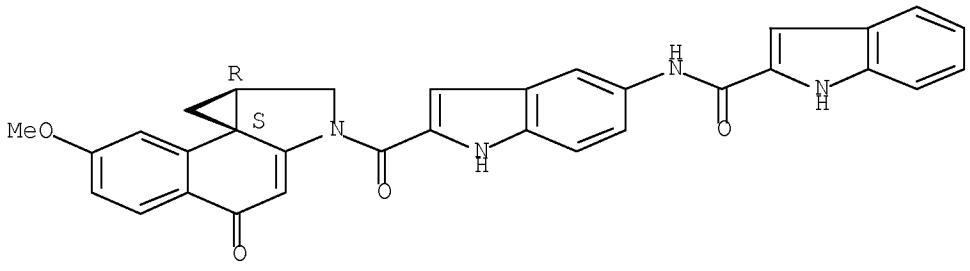
RN 173655-27-1 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[(9,9a-dihydro-7-methoxy-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1H-indol-5-yl]-, (8bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 173655-28-2 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[(9,9a-dihydro-7-methoxy-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1H-indol-5-yl]-, (8bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



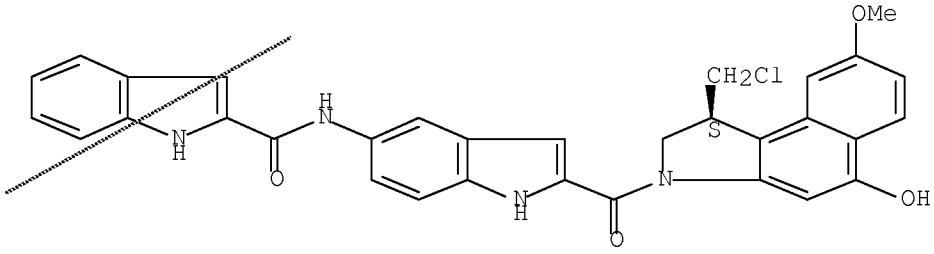
IT 173483-78-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and DNA alkylating activity of MCBI analogs of CC-1065 and the duocarmycins)

RN 173483-78-8 CAPLUS

CN 1H-Indole-2-carboxamide, N-[2-[[1-(chloromethyl)-1,2-dihydro-5-hydroxy-8-methoxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L14 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1997:366275 CAPLUS Full-text

DOCUMENT NUMBER: 126:330520

ORIGINAL REFERENCE NO.: 126:64239a,64242a

TITLE: Preparation of analogs of CC-1065 and the duocarmycins, containing the cyclopropa[c]benz[e]indol-4-one subunit, for use as antitumor agents

INVENTOR(S): Boger, Dale L.

PATENT ASSIGNEE(S): Scripps Research Institute, USA; Boger, Dale L.

SOURCE: PCT Int. Appl., 140 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9712862	A1	19970410	WO 1996-US16481	19961003
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG				
CA 2233936	A1	19970410	CA 1996-2233936	19961003
AU 9674315	A	19970428	AU 1996-74315	19961003
AU 727608	B2	20001214		
EP 862553	A1	19980909	EP 1996-936498	19961003
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 11513391	T	19991116	JP 1996-514522	19961003
NZ 321172	A	20000228	NZ 1996-321172	19961003
US 6548530	B1	20030415	US 1998-51264	19981002
US 20040002528	A1	20040101	US 2003-417043	20030415

US 20050032860 A1 20050210 US 2004-876992 20040624
PRIORITY APPLN. INFO.: US 1995-4752P P 19951003
WO 1996-US16481 W 19961003
US 1998-51264 A1 19981002
US 2003-417043 B1 20030415

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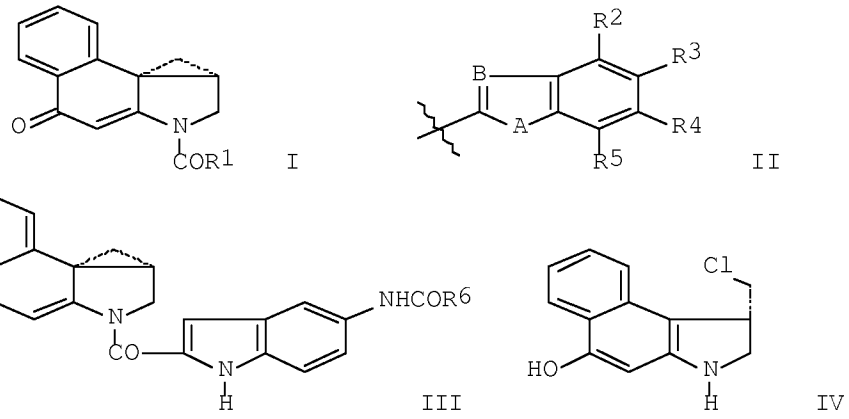


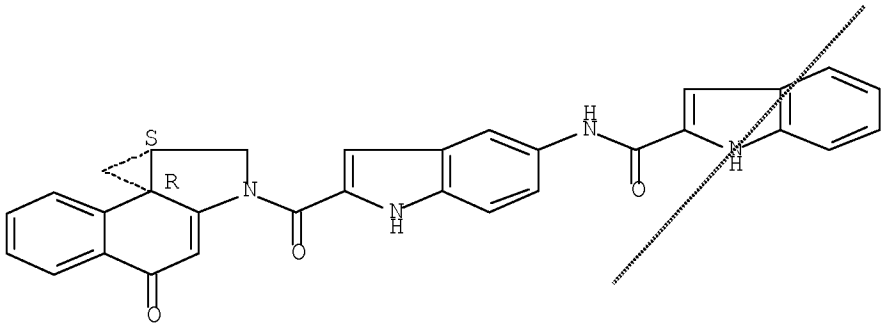
AB Analogs I [R1 = alkyl, amino, alkyloxy, hydrazinyl, radical (II); A = NH, O; B = C, N; R2R3 = vinylene group; R2-R3 = H, OH, alkyl, alkyloxy, pyrrolidinyl; R4-R5 = H, OH, alkyl, alkyloxy] of the antibiotics CC-1065 and the duocarmycins, contg. the 1,2,9,9a-tetrahydrocyclopropa[c]benz[e]in dol-4-one (CBI) alkylation subunit, where prepd. and shown to have potent cytotoxic activity and use as antitumor agents. Thus, amide III (R6 = 2-indolyl) was prepd. starting from Me 5-nitro-2-indolecarboxylate, 2-indolecarboxylic acid and arom. alc. IV and had an IC50 value of 10 pM when tested against L1210 cells. A direct relationship between functional stability and in vitro cytotoxic potency was shown. The CBI-based analogs were easily synthesized and were 4X more stable and 4X more potent than the corresponding analogs contg. the authentic CPI alkylation subunit of CC-1065 and comparable in potency to agents contg. the authentic alkylation subunit of duocarmycin SA. Similarly, the CBI-based agents alkylate DNA with an unaltered sequence selectivity at an enhanced rate and with a greater efficiency than the corresponding CPI analog and were comparable to the corresponding analog incorporating the duocarmycin SA alkylation subunit. Systematic and extensive modifications and simplifications in the DNA binding subunits attached to CBI were also described.

IT 135306-52-4P 141781-45-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of analogs of CC-1065 and the duocarmycins, contg. the cyclopropa[c]benz[e]indol-4-one subunit, for use as antitumor agents)

RN 135306-52-4 CAPLUS

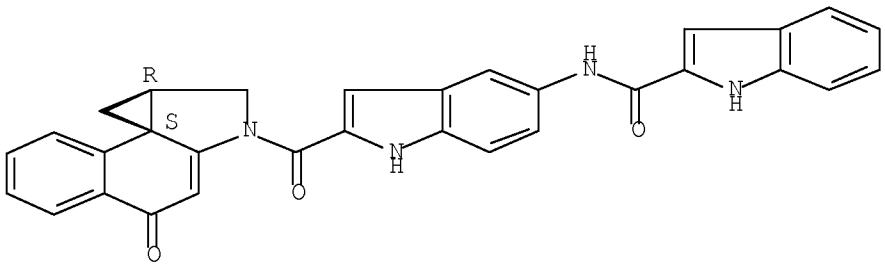
CN 1H-Indole-2-carboxamide, N-[2-[[(8bR,9aS)-9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



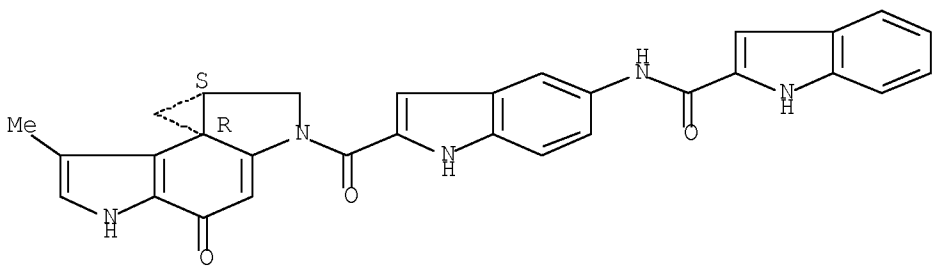
RN 141781-45-5 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[(9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1H-indol-5-yl]-, (8bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



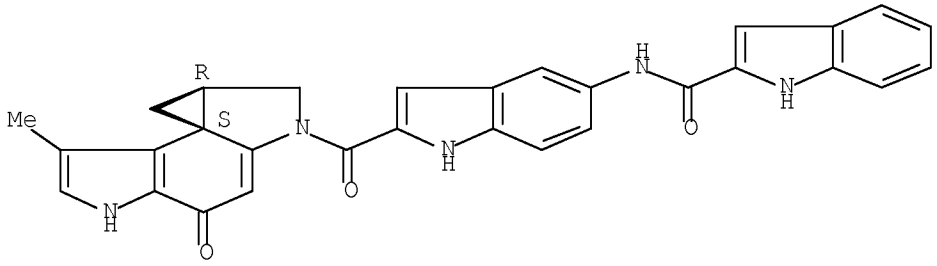
IT 101222-80-4, (+)-U 71184 104713-39-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of analogs of CC-1065 and the duocarmycins, contg. the cyclopropa[c]benz[e]indol-4-one subunit, for use as antitumor agents)
RN 101222-80-4 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[(7bR,8aS)-4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 104713-39-5 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[(7bS,8aR)-4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

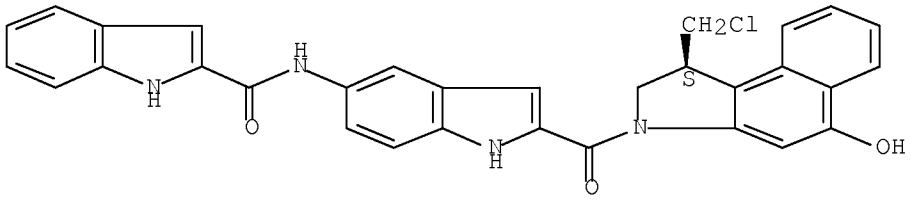
Absolute stereochemistry. Rotation (-).



IT 135306-53-5P 172375-73-4P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of analogs of CC-1065 and the duocarmycins, contg. the cyclopropa[c]benz[e]indol-4-one subunit, for use as antitumor agents)

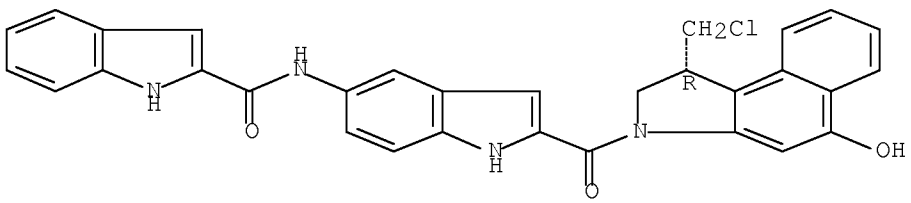
RN 135306-53-5 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[(1S)-1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

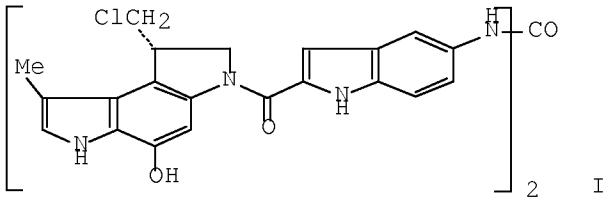


RN 172375-73-4 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[1-(chloromethyl)-1,2-dihydro-5-hydroxy-3H-benz[e]indol-3-yl]carbonyl]-1H-indol-5-yl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L14 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1992:227757 CAPLUS Full-text
DOCUMENT NUMBER: 116:227757
ORIGINAL REFERENCE NO.: 116:38323a,38326a
TITLE: DNA interstrand cross-linking, DNA sequence specificity, and induced conformational changes produced by a dimeric analog of (+)-CC-1065
AUTHOR(S): Ding, Z. M.; Hurley, L. h.
CORPORATE SOURCE: Coll. Pharm., Univ. Texas, Austin, TX, 78712, USA
SOURCE: Anti-Cancer Drug Design (1991), 6(5), 427-52
CODEN: ACDDEA; ISSN: 0266-9536
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB U-77779 (I) is a sym. dimer of the spirocyclopropyl alkylating subunit of (+)-CC-1065 in which the linker consists of two indole subunits sepd. by a ureido group. This compd. was synthesized by Upjohn and found to be more active in both antitumor efficacy and cytotoxicity than its mono-alkylating analogs. Using three different 21-base pair DNA duplexes contg. I reactive sequences, the authors have shown that I produces a stable interstrand cross-linked species that loses its internal self complementarity. A comparison of I with the mono- alkylating analogs of (+)-CC-1065 shows that it appears to have an increased sequence selectivity such that, while monoalkylating compds. like (+)-CC-1065 react at more than one site, I reacts only at sites where there are two suitably positioned alkylation sites. Chem. footprinting with 1,10-phenanthroline-copper complex revealed a six base pair cross-linked region between the two covalently modified adenines with modulated cleavage outside this region. In the case of hydroxyl radical footprinting, considerable variability of the extent of cleavage within the cross-linked sequence was found. These results are discussed in terms of likely induced conformational changes in DNA. In contrast to (+)-CC-1065, non-denaturing gel electrophoresis did not reveal any net bending of DNA due to I, which the authors believe is due to the 180.degree. out-of-phase bending produced on opposite strands of DNA by the cross-linker.

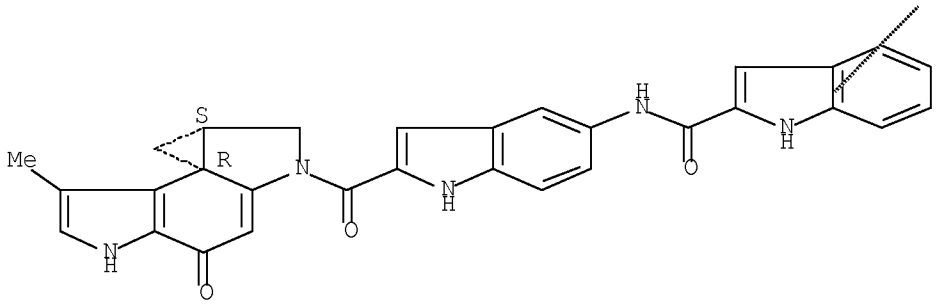
IT 101222-80-4, (+)-ABC 129655-21-6, U 77779
RL: BIOL (Biological study)
(DNA crosslinking by, sequence specificity and conformational changes in relation to)

RN 101222-80-4 CAPLUS

CN 1H-Indole-2-carboxamide, N-[2-[[(7bR,8aS)-4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]-

(CA INDEX NAME)

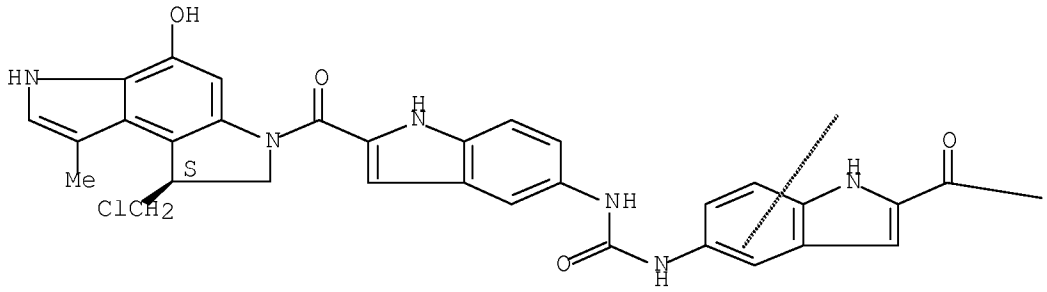
Absolute stereochemistry. Rotation (+).



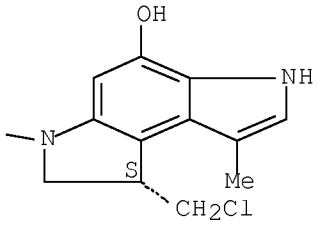
RN 129655-21-6 CAPLUS
CN Urea, N,N'-bis[2-[[(1S)-1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methylpyrrolo[3,2-e]indol-3(2H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

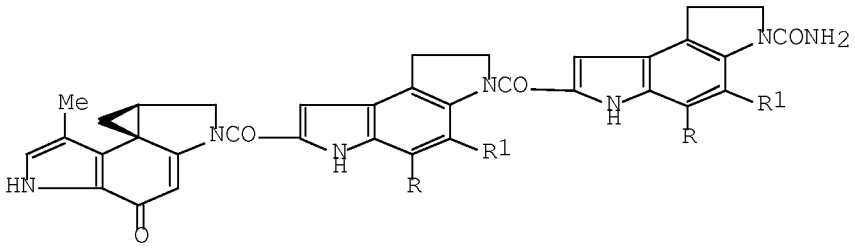


PAGE 1-B

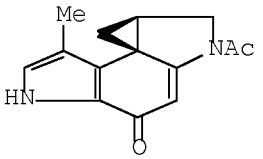


L14 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1990:458759 CAPLUS Full-text

DOCUMENT NUMBER: 113:58759
ORIGINAL REFERENCE NO.: 113:9930h,9931a
TITLE: Sequence specificity of DNA alkylation by the unnatural enantiomer of CC-1065 and its synthetic analogs
AUTHOR(S): Hurley, Laurence H.; Warpehoski, Martha A.; Lee, Chong Soon; McGovren, J. Patrick; Scahill, Terrence A.; Kelly, Robert C.; Mitchell, Mark A.; Wicnienski, Nancy A.; Gebhard, Ilse; et al.
CORPORATE SOURCE: Coll. Pharm., Univ. Texas, Austin, TX, 78712, USA
SOURCE: Journal of the American Chemical Society (1990), 112(12), 4633-49
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 113:58759
GI



I



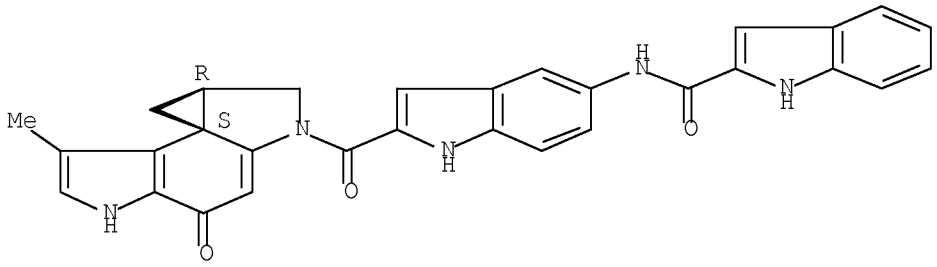
IV

AB (-)-CC-1065, (I, R = OMe, R1 = OH; II), the unnatural enantiomer of the potent and sequence-selective, DNA-reactive antibiotic, (+)-CC-1065 (III), was prepd. and its covalent reaction with DNA was studied and compared to that of III. Although II also formed covalent adducts in which the cyclopropyl C was bonded to the N-3 atom of adenine, and the thermal strand breakage that it produced paralleled that seen for III, it lay in the opposite direction along the minor groove and exhibited a markedly different sequence requirement for the covalently modified adenine. While II and its analog, (-)-AB'C' (I, R = R1 = H), reacted readily at adenines near to, but generally distinct from, adenines affected by III, and exhibited potent cytotoxicity, their simpler analogs did not alkylate DNA under the conditions employed and were biol. nonpotent. At relatively high concns., the smallest such analog, (-)-A, (IV) reacted detectably only at the same sites selected by III. An anal. of the reactivity patterns of II and III and their analogs with DNA restriction fragments supported the conclusion that the mode of sequence recognition for II adduct formation is fundamentally different from that of III and is primarily controlled by specific minor groove, AT-selective binding interactions, rather than by sequence requirements of the covalent step, as occurs for III and the (+)-CPI analogs. Models are proposed comparing the interactions of the enantiomeric alkylating moieties variously oriented in the minor groove at potential reaction sites. The evolutionary significance of both the

alkylating moiety and the minor groove binding segments of the natural product is discussed.

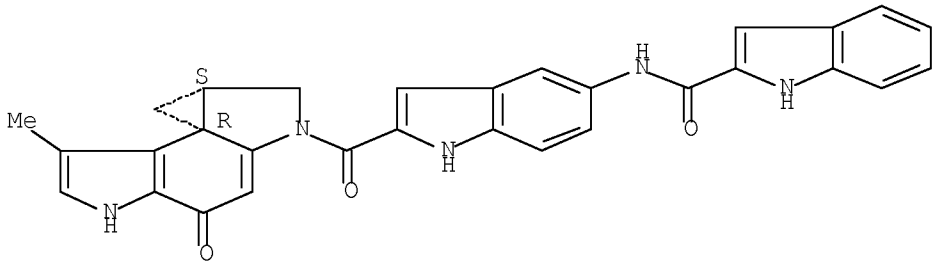
IT 104713-39-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(DNA alkylation by)
RN 104713-39-5 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[(7bS,8aR)-4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]-
(CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



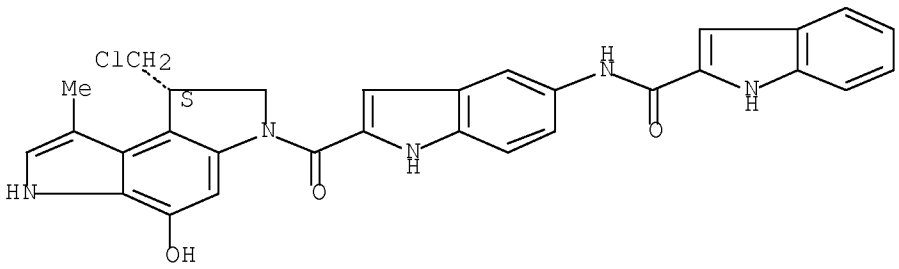
IT 101222-80-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and DNA alkylation by)
RN 101222-80-4 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[(7bR,8aS)-4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]-
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 110314-46-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and cyclization of)
RN 110314-46-0 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[1-(chloromethyl)-1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl]-, (S)-
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



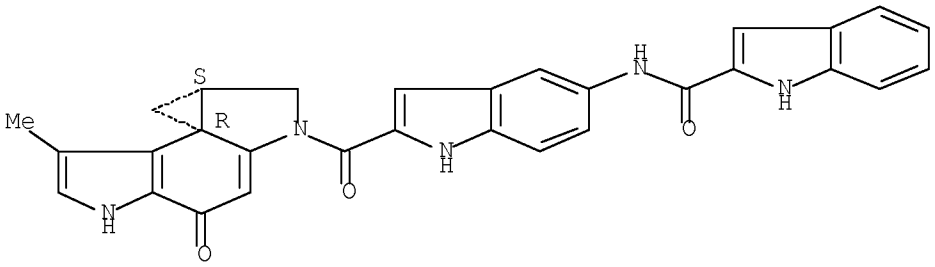
L14 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1989:50743 CAPLUS Full-text
DOCUMENT NUMBER: 110:50743
ORIGINAL REFERENCE NO.: 110:8201a,8204a
TITLE: Evaluation of DNA binding characteristics of some CC-1065 analogs
AUTHOR(S): Swenson, David H.; Petzold, Gary L.; Williams, Marta G.; Li, Li H.; Prairie, Mark D.; Krueger, William C.
CORPORATE SOURCE: Karkinos Biochem. Inc., Phoenix, AZ, 85040, USA
SOURCE: Chemico-Biological Interactions (1988), 67(3-4), 199-213
CODEN: CBINA8; ISSN: 0009-2797
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The factors influencing the binding of the antitumor antibiotic CC-1065 to DNA were examd. using racemic analogs with varying chain lengths. The ability of these agents to bind DNA appeared to be related to cytotoxic potency; however, this did not appear to be a direct quant. correlation. Two enantiomers of a bis-indole analog of CC-1065 were studied for DNA binding and cytotoxic activity. The agent with the same stereochem. configuration as CC-1065 was a potent cytotoxin, but its enantiomer was essentially inactive. Both enantiomers showed significant binding to DNA, but the biol. less active isomer showed less overall binding. In all cases, the agents preferred AT-rich DNA, and all bound to similar regions in DNA as evidenced by positions of drug-initiated thermal breaks in single end-labeled fragments of .vphi.X 174RF DNA. The overall similarity in site specificity for binding of the structurally diverse agents suggests that much of the specificity obsd. in binding of the agent to DNA lies in the DNA itself. Thus, it may be difficult to change minor groove specificity for agents of this type simply by designing structures that can encompass guanine or cytosine residues. Other modifications, such as changing the specificity of the alkylating moiety, may be required to achieve this goal.

IT 101222-80-4 104713-39-5 104713-40-8
RL: BIOL (Biological study)
(DNA binding by)

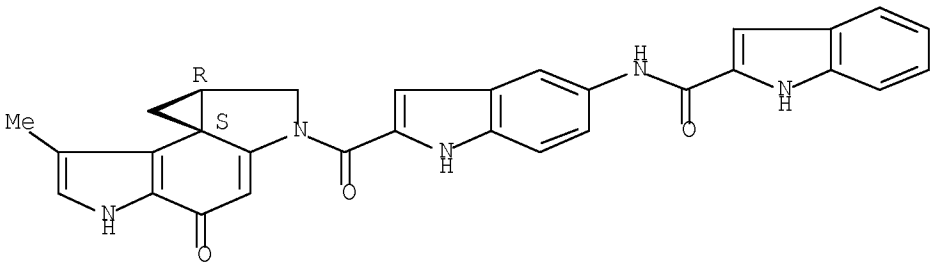
RN 101222-80-4 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[(7bR,8aS)-4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

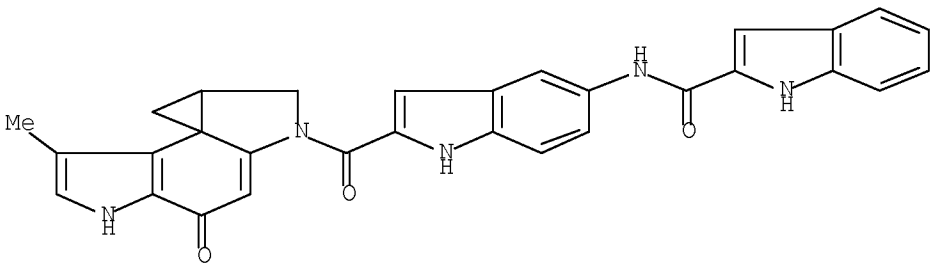


RN 104713-39-5 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[(7bS,8aR)-4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 104713-40-8 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)



L14 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1988:400212 CAPLUS Full-text
DOCUMENT NUMBER: 109:212
ORIGINAL REFERENCE NO.: 109:31a,34a
TITLE: Molecular basis for sequence-specific DNA

alkylation by CC-1065

AUTHOR(S): Hurley, Laurence H.; Lee, Chong Soon; McGovren, J. Patrick; Warpehoski, Martha A.; Mitchell, Mark A.; Kelly, Robert C.; Aristoff, Paul A.
CORPORATE SOURCE: Coll. Pharm., Univ. Texas, Austin, TX, 78712, USA
SOURCE: Biochemistry (1988), 27(10), 3886-92
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

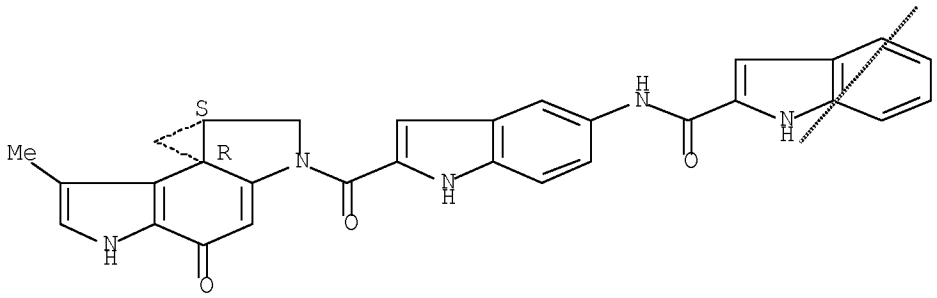
AB The DNA alkylation, sequence specificity, and biol. potency of (+)-CC-1065 (I) and a select group of trimeric synthetic analogs were evaluated. The results suggest that (a) noncovalent interactions between this series of compds. and DNA do not lead to the formation of complexes stable enough to be detected by footprinting methods; (b) sequence specificity and alkylation intensity can be modulated by the substituents on the nonreactive middle and right-hand segments; and (c) biol. potency correlates well with ability to alkylate DNA. In addn., the extent and the sequence specificity of covalent adduct formation between linear DNA fragments and 3 analogs (II-IV) comprised of the CC-1065 I alkylating subunit linked to 0, 1, or 2 nonreactive indole subunits were compared. The results suggest that specificity of covalent binding of this analog series is controlled not by the noncovalent interactions of the indole subunits with the minor groove but by sequence-dependent reactivity of adenines with the alkylating subunit. However, the other 2 subunits markedly increase the apparent rate const. of the reaction with "susceptible" adenines, suggesting that these moieties facilitate noncovalent interactions preceding covalent bond formation. These and other results provide strong exptl. evidence for the importance of sequence-dependent site reactivity, rather than noncovalent minor groove interactions, in detg. the alkylation specificity of some DNA -reactive mols.

IT 101222-80-4 114251-20-6
RL: BIOL (Biological study)
(DNA alkylation and tumor inhibition by)

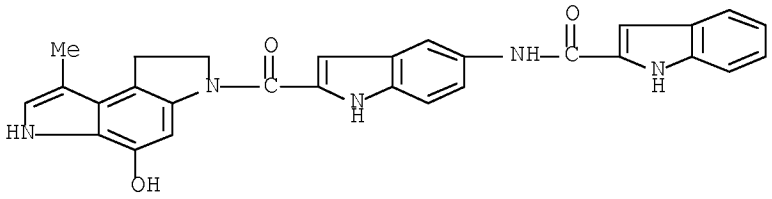
RN 101222-80-4 CAPLUS

CN 1H-Indole-2-carboxamide, N-[2-[[(7bR,8aS)-4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 114251-20-6 CAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[(1,6-dihydro-5-hydroxy-8-methylbenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl)carbonyl]-1H-indol-5-yl]- (9CI) (CA INDEX NAME)



=>

=>
Executing the logoff script...

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	77.04	598.03

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-9.60	-29.60

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 22:16:08 ON 08 JUL 2008